



**BlueCross BlueShield
of Alabama**

**Nuvigil® /armodafinil,
Provigil® /modafinil
Prior Authorization
with Quantity Limit Criteria
Program Summary**

This program applies to Commercial, GenPlus, and Health Insurance Marketplace formularies. Commercial and Health Insurance Marketplace formularies target all agents. GenPlus formulary only targets modafinil, all other agents are non-formulary.

OBJECTIVE

The intent of the Nuvigil/armodafinil, Provigil/modafinil Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling (one tablet per day). The PA criteria will approve modafinil or armodafinil when prescribed according to product labeling for patients 17 years and older. Requests for modafinil or armodafinil will be reviewed when patient-specific documentation has been provided. The PA criteria will approve only one of these agents at a time. Brand and generic products are included in this program.

TARGET DRUGS

Nuvigil (armodafinil)

Provigil (modafinil)^a

a – generic available, subject to prior authorization program

PROGRAM QUANTITY LIMIT

Brand (generic)	GPI	Multisource Code	Quantity Per Day Limit
Nuvigil/armodafinil			
50 mg tablet	61400010000310	M, N, O, or Y	1 tablet
150 mg tablet	61400010000330	M, N, O, or Y	1 tablet
200 mg tablet	61400010000335	M, N, O, or Y	1 tablet
250 mg tablet	61400010000340	M, N, O, or Y	1 tablet
Provigil/modafinil^a			
100 mg tablet	61400024000310	M, N, O, or Y	1 tablet
200 mg tablet	61400024000320	M, N, O, or Y	1 tablet

a – generic available, subject to quantity limit

PRIOR AUTHORIZATION WITH QUANTITY LIMIT CRITERIA FOR APPROVAL

Nuvigil/armodafinil, Provigil/modafinil will be approved when ALL of the following are met:

1. The patient is 17 years of age or older
AND
2. The patient’s diagnosis is narcolepsy, obstructive sleep apnea/hypopnea syndrome, or shift work sleep disorder
AND
3. The patient does not have any FDA labeled contraindications to the requested agent
AND
4. The patient is receiving only one of the listed agents – Nuvigil/armodafinil OR Provigil/modafinil
AND
5. ONE of the following:
 - a. The quantity requested is less than or equal to the program quantity limit

OR

- b. The quantity (dose) requested is above the program limit, less than or equal to the maximum dose recommended in FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength

OR

- c. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 12 months

FDA Labeled Contraindications

Agent	Contraindication(s)
Nuvigil (armodafinil)	known hypersensitivity to modafinil, armodafinil or its inactive ingredients
Provigil (modafinil)	known hypersensitivity to modafinil, armodafinil or its inactive ingredients

FDA APPROVED INDICATIONS AND DOSAGE^{1,2}

Available Products	FDA Approved Indications			
	Narcolepsy	OSAHS	SWD	Dosing and Administration
Nuvigil* (armodafinil)	✓	✓	✓	OSAHS/Narcolepsy: 150-250 mg/day; in OSAHS, there is no consistent evidence that doses >150 mg/day provide greater benefit SWD: 150 mg/day
Provigil* (modafinil)**	✓	✓	✓	OSAHS/Narcolepsy/SWD: 200 mg/day; doses up to 400 mg/day have been well tolerated but there is no consistent evidence that this dose provides benefit beyond that of the 200 mg dose

OSAHS= obstructive sleep apnea/hypopnea syndrome, SWD=shift work disorder

*Safety and effectiveness in pediatric patients below age 17 have not been established. Serious skin rashes, including erythema multiforme major and Stevens-Johnson Syndrome have been associated with modafinil use in pediatric patients.

** generic available

CLINICAL RATIONALE

Modafinil and armodafinil are used to treat narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. Modafinil and armodafinil have a lower potential for abuse (Schedule IV) than other medications that induce alertness; dextroamphetamine and methylphenidate are Schedule II.⁴

Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS)

Recommendations for treatment of OSAHS include behavioral measures (e.g., weight loss, altered sleeping position, avoidance of alcohol and sedatives). The mainstay of therapy for OSAHS is administration of continuous positive airway pressure (CPAP). Oral appliances may benefit patients who are unable or unwilling to use CPAP or other forms of positive air pressure therapy.³

Guidelines from the American College of Physicians (ACP, 2013) on management of OSAHS do not include modafinil/armodafinil in their recommendations for treatment. ACP guidelines state that pharmacologic therapy is not currently supported by evidence and should not be prescribed for OSA treatment.³⁰

A review on the treatment of OSA suggested pharmacologic agents play a minimal role in the treatment of breathing itself in patients with a sleep disorder; CPAP is the primary therapy for the breathing. Excessive sleepiness can persist despite effective CPAP therapy. Modafinil and armodafinil are considered adjunctive therapies to improve wakefulness in these patients. These agents are recommended for patients who experience residual sleepiness despite optimal CPAP therapy, provided CPAP compliance is closely monitored. Modafinil or armodafinil do not treat the OSAHS itself but only the associated symptoms of sleepiness. The majority of patients (75%) with severe sleepiness at baseline still had mean multiple sleep latency times of less than 10 minutes despite the addition of modafinil to effective therapy with CPAP. This suggests that these drugs do not necessarily eliminate the risk of motor vehicle and other accidents in the OSAHS population. Concern also exists that the use of pharmacotherapy to treat excessive sleepiness associated with OSAHS may lead to subsequent reduction in CPAP compliance.⁴

Shift Work Sleep Disorder

According to the American Academy of Sleep Medicine (AASM), shift work refers to non-standard work schedules, including permanent or intermittent night work, early morning work, and rotating schedules. A formal diagnosis of SWSD has rarely been used in research studies. The validity and reproducibility of the diagnostic criteria for SWSD needs testing, and the

boundary between a normal and a pathological response to circadian stress of unnatural sleep schedules associated with shift work remains unclear.^{5,6}

Recommended AASM treatments for SWSD disorders include: planned sleep schedules, timed light exposure, timed melatonin administration, hypnotics, stimulants [e.g., caffeine], and alerting agents [e.g., modafinil]. Studies using psychostimulants (modafinil, caffeine, and methamphetamine) for SWSD have shown efficacy in countering sleepiness and improving psychomotor performance during the night shift compared with placebo. Modafinil and caffeine in medical doses have established safety records so in most cases when enhanced alertness is necessary, the benefits are considered to outweigh the risks for this application. Stimulants have not been shown to be a safe substitute for adequate sleep.^{5,6}

A systematic review (2014) evaluated pharmacologic interventions for sleepiness and sleep disturbances due to SWSD: Analysis included 15 RCTs (N=715) using melatonin, modafinil, armodafinil, or caffeine. Armodafinil taken before the night shift probably reduces sleepiness by one point on the Karolinska Sleepiness Scale (KSS) and increases alertness by 50 ms in a simple reaction time test at three months' follow-up in shift work sleep disorder patients. Modafinil probably has similar effects on sleepiness (KSS) and alertness in the psychomotor vigilance test in the same patient group. Post-marketing, severe skin reactions have been reported. Adverse effects reported by trial participants were headache, nausea and a rise in blood pressure. Authors concluded modafinil and armodafinil increase alertness and reduce sleepiness to some extent in SWSD but are associated with adverse events.³¹

Another systematic review (JAMA, 2015) also evaluated pharmacological interventions for sleepiness and sleep disturbances caused by shift work (15 RCTs; N=1240). Modafinil was associated with small benefit and frequent adverse outcomes.³⁸

Narcolepsy

Modafinil is often referred to as the first line treatment for narcolepsy in reviews^{32,33} and guidelines³⁴, but may not be effective in some patients. Traditional stimulant drugs (amphetamines, methylphenidate) are also frequently effective in treatment of EDS in narcolepsy.^{32,33}

A review (2015) suggests current treatments available for narcolepsy are often unsatisfactory due to suboptimal efficacy, troublesome side effects, development of drug tolerance, and inconvenience. The pharmacotherapeutic approach is based on symptom control, and includes newer drugs supported by RCT evidence (e.g., modafinil, armodafinil) and compounds which have not been assessed in robust studies but are known for efficacy (e.g., methylphenidate, amphetamines). Amphetamines and methylphenidate previously were the mainstay of EDS management and are still widely used. They are generally well tolerated, but minor sympathomimetic side effects are common. Cardiovascular side effects may prevent use in some patients (e.g. elderly or other relevant comorbidities). Long-term use has been linked to adverse psychological events. Abuse of amphetamine derivatives in well-defined narcolepsy subjects is rare, but tolerance can develop in up to a third of patients. Modafinil and armodafinil are generally less potent. However, favorable safety profiles and higher-level supportive evidence result in the recommendation for these agents as first-line treatment for EDS of narcolepsy.³⁷

A European review (2012) found recent drug trials reflected pharmaceutical sponsorship, and only considered the newer wakefulness promoting drugs for treatment of narcolepsy (modafinil or sodium oxybate). All anti-narcolepsy medications improve the symptoms of sleepiness rather than returning patients to full and sustained alertness. Despite short-term efficacy, long term studies have not been conducted; there is little information to show which patients switch from newer agents to traditional, amphetamine-based wakefulness medications.¹¹

A U.S. review (2012) suggested methylphenidate is more effective and potent than modafinil and of lower cost. Various preparations and formulations can have different interindividual effects. As a base preparation, immediate release methylphenidate (5–10 mg) can be helpful, either to alleviate sleep drunkenness in hypersomnia, to bridge gaps in alertness during the daytime (postprandial dose), or to use when necessary in case of emergency (e.g. need to drive to the hospital). Amphetamine is used similar to methylphenidate, preferably using long-lasting formulations, and can be more effective than methylphenidate in some patients. Monitoring of pulse and blood pressure is needed. Modafinil may be considered as a first intention treatment due to fewer side effects, and lower addictive potential, but is less efficacious than amphetamine or methylphenidate. Headache is a common side effect, potentially avoidable by increasing the dose slowly. Possible allergic side effects should be monitored, notably in children.²⁸

The Medical Letter (2010) suggested armodafinil has not been shown to offer any clinical advantage over the racemic mixture (modafinil). Both are modestly effective in maintaining daytime alertness, apparently without disrupting nighttime sleep. Severe angioedema, multi-organ hypersensitivity reactions and Stevens-Johnson syndrome have occurred.²⁹

The American Academy of Sleep Medicine Practice Parameters (2007) also reflected the shift toward investigation and reporting of newer agents, mostly supported by the pharmaceutical industry, which is in contrast to the widespread use of traditional stimulants in the U.S. Clinical practice patterns suggest modafinil is currently viewed as the initial drug of choice for treatment of excessive sleepiness due to narcolepsy. However, there are no data to indicate what proportion of patients treated initially with modafinil require transition to traditional stimulants, to sodium oxybate, or to combination therapy.⁶ There is a need for randomized trials that compare the newer agents to the traditional stimulants to establish relative efficacy and safety of these agents.⁶⁻⁸

Although supporting evidence from randomized controlled trials is less than for the newer agents, the traditional stimulants (e.g., amphetamine, dextroamphetamine, methylphenidate) are considered mainstays of treatment for sleepiness associated with narcolepsy. There have been three level 2 studies (e.g. randomized trials with methodological flaws) and four level 5 studies (e.g. case series) that support the efficacy of traditional stimulants for treatment of sleepiness in narcolepsy.⁶

Off-Label Use

There are many reports and ongoing studies of off-label use (jet lag, fatigue, depression, schizophrenia, etc.) for modafinil and armodafinil. Although there may be potential clinical benefits for some of these uses in certain patients, current data is generally limited and conflicting, and the benefit-risk profile of these agents for off-label use is unclear.

Although there are studies that have shown modafinil had benefit over placebo in off-label treatment of Attention Deficit Hyperactivity Disorder, there were three cases of serious rash including one case of possible Stevens-Johnson Syndrome among the 933 patients exposed to modafinil in these studies. Prescribing information for modafinil and armodafinil emphasizes the risk of serious rashes, some requiring hospitalization and discontinuation of treatment, in adults and children on either drug. The FDA also has clinical study and postmarketing reports providing evidence of serious skin and hypersensitivity reactions especially with pediatric use associated with modafinil. Since armodafinil is the R-enantiomer of modafinil, there is concern with both drugs. Modafinil and armodafinil are not approved for use in pediatric patients for any indication. The FDA released their statement regarding use in pediatric patients in November 2007 and labeling changes occurred in October 2010. Studies regarding the efficacy of modafinil for the treatment of ADHD in children predate the warning statement by the FDA.^{1,2,9,10,12}

Studies of modafinil and armodafinil as adjunctive therapy in major depressive disorder (MDD) and bipolar I disorder have yielded promising results. One small study (n=46) in patients in Iran found that modafinil enhanced the antidepressant effect of fluoxetine.¹³ In two larger studies, an 8-week and a 6-week randomized, double-blind placebo control trial, patients with MDD and partial response to antidepressant therapy demonstrated a significant improvement in sleepiness and fatigue in the first 1 to 2 weeks of the studies. However, this improvement failed to remain significant by the final visits (end of 8 or 6 weeks depending on trial).^{14,15} A randomized, double-blind, placebo-controlled study of armodafinil as adjunctive therapy for major depressive episodes in 257 patients with bipolar I disorder demonstrated a significant improvement in depressive symptoms in patients treated adjunctively with armodafinil as compared to the placebo group.¹⁶ However, the authors of these trials agree that more studies are needed to establish the role of modafinil and armodafinil as adjunctive therapy in MDD and bipolar I disorder. Specifically, optimal modafinil dosing regimens need to be established and augmentation in patients with greater symptom severity (i.e. HAM-D-17 \geq 14 at pretreatment) needs to be studied.¹⁴⁻¹⁶

The American Psychiatric Association has the following statement regarding the use of additional therapies for depression treatment augmentation, "Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant, omega-3 fatty acids, folate, or a psychostimulant medication, including modafinil. They rate modafinil as [III], meaning that modafinil may be recommended on the basis of individual circumstances."²⁶ There is no mention in NICE guidelines (United Kingdom) of adjunctive therapy with modafinil, armodafinil, or any other psychostimulant medication.²⁷

The studies regarding the use of modafinil and armodafinil as adjunctive therapy in schizophrenia have been less promising and often conflicting. These studies have been small (n < 50) and often have shown no benefit for the negative and cognitive symptoms in schizophrenia. One study involving 20 patients (16 of which were male) demonstrated small improvements in cognition, based on a variety of tests, in patients given a one-time dose of modafinil 200 mg or placebo.¹⁷ An additional study in 19 patients demonstrated enhanced activity in the anterior cingulate cortex in patients given a single dose of modafinil 100mg. There was no correlation between brain activity and working memory.¹⁸ No studies to date have demonstrated any benefit of adjunctive armodafinil in schizophrenia.¹⁹⁻²¹

A 9-week, single blind study conducted in 2001 demonstrated significant improvement in multiple sclerosis (MS)-related fatigue in patients taking modafinil 200mg daily. This 9-week study was conducted in 72 patients, the majority of which had the relapsing-remitting form of MS, and 5 patients reported a worsening of their MS which was possibly related to the modafinil.²⁴ While this study demonstrated a potential use for modafinil in MS-related fatigue, subsequent studies have failed to yield the same positive results.^{22,23,25} The European Medicines Agency in 2010 recommended that modafinil be only used for the treatment of sleepiness associated with narcolepsy. On the basis of the available data the European Medicines Agency Committee concluded that the benefits of modafinil only outweighed their risks in the therapeutic indication narcolepsy, a chronic sleep disorder characterized by excessive daytime sleepiness. For all other indications the Committee found that the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. Therefore, the Committee concluded that all other indications should be withdrawn from the marketing authorizations of these medicines.³⁶ Micromedex does not recommend use of modafinil in MS fatigue.³⁹

A database study (JAMA Intern Med, 2013) suggested patients receiving modafinil without an on label diagnosis increased by 15-fold while those with an on-label diagnosis increased by only 3-fold (period 2002-2009). Authors suggest modafinil is often being used in patients with comorbid conditions and concurrent medications that do not reflect the populations that

formed the basis for regulatory approval. This raises concerns about the potential for adverse events and indicates the need for further study of unapproved indications.³⁵

Safety

Armodafinil and modafinil are contraindicated in patients with known hypersensitivity to armodafinil or modafinil. Armodafinil and modafinil are Schedule IV controlled substances.^{1,2}

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